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Predictors of Super-Response to Cardiac Resynchronization Therapy and Associated Improvement in Clinical Outcome

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Study

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Objectives The authors investigated predictors of left ventricular ejection fraction (LVEF) super-response to cardiac resynchronization therapy with defibrillator (CRT-D) and whether super-response translated into improved event-free survival in patients with mildly symptomatic heart failure (HF).

Background Few data exist on predictors of super-response to CRT-D and associated morbidity and mortality in mildly symptomatic HF populations.

Methods Patients were assigned to CRT-D with paired echocardiograms at baseline and at 12 months (n = 752). Super-response was defined by the top quartile of LVEF change. Best-subset regression analysis identified predictors of LVEF super-response. Kaplan-Meier survival analysis and Cox proportional hazards regression were performed to investigate associations of response category with development of nonfatal HF event or all-cause death.

Results All 191 super-responders experienced an LVEF increase of ≥14.5% (mean LVEF increase 17.5 ± 2.7%). Six predictors were associated with LVEF super-response to CRT-D therapy: female sex (odds ratio [OR]: 1.96; $p = 0.001$), no prior myocardial infarction (OR: 1.80; $p = 0.005$), QRS duration ≥150 ms (OR: 1.79; $p = 0.007$), left bundle branch block (OR: 2.05; $p = 0.006$), body mass index <30 kg/m^2 (OR: 1.51; $p = 0.035$), and smaller baseline left atrial volume index (OR: 1.47; $p < 0.001$). Cumulative probability of HF or all-cause death at 2 years was 4% in super-responders, 11% in responders, and 26% in hypo-responders (log-rank $p < 0.001$ overall). In multivariate analysis, hyporesponse was associated with increased risk of HF or all-cause death, compared with super-response (hazard ratio: 5.25; 95% confidence interval: 2.01 to 13.74; $p = 0.001$).

Conclusions Six baseline factors predicted LVEF super-response in CRT-D–treated patients with mild HF. Super-response was associated with reduced risk of subsequent cardiac events. (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol 2012;59: 2366–73) © 2012 by the American College of Cardiology Foundation

Biventricular pacing with cardiac resynchronization therapy (CRT) and CRT with defibrillator (CRT-D) have been shown to improve heart failure (HF) morbidity, quality of life, and survival in those with reduced left ventricular ejection fraction (LVEF), advanced HF symptoms, and increased QRS duration (1,2). Despite the overall improvement demonstrated in randomized controlled trials, up to 30% of patients do not exhibit improvements in New York

See page 2374

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Heart Association (NYHA) functional class or measures of left ventricular remodeling (3,4). Overall, the average expected improvement in absolute LVEF after CRT ranges from 3% to 5% (3,5).

There is wide variability in the extent of LV remodeling and improvement in LVEF with CRT. Recent studies have indicated that certain patients, referred to as "super-responders," may derive dramatic improvements, including near normalization of LVEF (6,7). These and other studies have identified patient characteristics associated with super-response to CRT such as left bundle branch block (LBBB), smaller LV and left atrial (LA) dimensions, greater LV strain, shorter duration of HF symptoms, and nonischemic cardiomyopathy (6–10). However, these relatively small studies conducted follow-up echocardiographic assessment of LVEF response at only 6 months post-implantation. Additionally, the majority of patients had moderate to severe HF symptoms (NYHA class III and IV), according to CRT implantation guidelines in place at the time of these studies.

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study recently showed that treatment with prophylactic CRT-D reduced the risk of nonfatal HF or death in patients with LVEF of ≤30%, QRS duration of ≥130 ms, and less severe HF symptoms (NYHA class I or II) compared with patients receiving implantable cardioverter-defibrillator (ICD) only (11). By assessing a large population of patients undergoing CRT-D therapy with longer echocardiographic follow-up (at 12 months) in this study, we sought to define patient characteristics that predict LVEF super-response to CRT in patients with mildly symptomatic (NYHA class I and II) HF. We also sought to investigate an association of LVEF super-response at 12 months with subsequent improvement in HF morbidity and survival.

Methods

Trial design. The MADIT-CRT design, study protocol, and primary results have been published previously (11,12). The trial enrolled 1,820 patients at 110 hospital centers between December 22, 2004, and April 23, 2008. Patients were randomly assigned in a 3:2 ratio to receive either CRT-D or ICD. All patients provided informed consent, including consent for echocardiographic analyses. The protocol was approved by the institutional review board at each participating center. The trial enrolled patients of either sex who were at least 21 years old with ischemic cardiomyopathy (NYHA class I or II) or nonischemic cardiomyopathy (NYHA class II only), sinus rhythm, an ejection fraction of ≤30%, and prolonged intraventricular conduction with a QRS duration of ≥130 ms. All patients met guideline indications for ICD therapy. Additional details on inclusion and exclusion criteria have been previously reported (11,12). The primary analysis included Cox proportional hazards regression for the outcome of nonfatal HF events or all-cause mortality.

Our study population consisted of 752 patients (69%) randomized to the CRT-D therapy group for whom we had complete information regarding clinical and echocardiographic data at baseline and at 12-month follow-up examination (with device on).

Abbreviations and Acronyms

BMI = body mass index
CRT = cardiac resynchronization therapy
CRT-D = cardiac resynchronization therapy with defibrillator
HF = heart failure
ICD = implantable cardioverter-defibrillator
LA = left atrial
LAVI = left atrial volume index
LBBB = left bundle branch block
LV = left ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

Echocardiographic methods. Echocardiograms were obtained according to the trial-specific protocol at baseline before device implantation (n = 1,089 in CRT-D group) and at 12-month follow-up. The Food and Drug Administration had originally requested that follow-up echocardiography be performed with CRT turned off; however, after the first 201 patients were tested under these conditions, the trial protocol was amended to allow follow-up echocardiography to be performed with CRT turned on. Paired echocardiograms from both baseline and 12-month follow-up while the device was turned on were available in 752 (69%) of those assigned to CRT-D. Echocardiographic images and data were sent to the echocardiographic core laboratory at the Brigham and Women's Hospital, where quality assessment was performed and LV, right ventricular, and LA measurements were made in all baseline and 12-month follow-up examinations as previously described (13).

Study design. Patients with paired echocardiograms were divided into quartiles of LVEF response based on change from baseline to 12-month follow-up echocardiograms with device on. Three groups based on response to CRT were defined and labeled "super-responders," "responders," or "hypo-responders." Super-response to CRT was defined by the highest quartile of LVEF change (n = 191), response by the second and third quartiles of LVEF change (n = 371), and hyporesponse by the lowest quartile of LVEF change (n = 190).

The primary endpoint for clinical outcome of the study was defined as nonfatal HF event or all-cause death, whichever came first. HF event diagnoses were made by physicians who were aware of study assignments, and the diagnoses required signs and symptoms consistent with HF responsive to intravenous decongestive therapy as an outpatient or oral or intravenous medications administered during a hospitalization. The secondary endpoints were defined as: 1) all-cause death; and 2) all-cause death or ICD therapy for ventricular tachycardia or ventricular fibrillation, whichever came first. Additional details on definitions of and therapy for ventricular arrhythmias have been previously reported (14). Adjudication of endpoints was carried out by independent committees unaware of study assignments, as described previously (11,12).

JACC Vol. 59, No. 25, 2012
June 19/26, 2012:2366–73

In the first stage of analysis, we identified predictors associated with LVEF super-response to CRT-D (with responders and hypo-responders categorized together as the reference group) among the 752 patients (69%) with available paired echocardiograms at baseline and at 12-month follow-up. In the second stage of the analysis, we performed a survival analysis of the primary and secondary endpoints by LVEF response category. Subsequently, we included the LVEF response variable in addition to all other variables to identify the strongest predictors associated with the primary endpoint of HF or all-cause death.

Statistical analysis. We included all clinical, electrocardiographic, echocardiographic, and laboratory covariates as potential predictors in the LVEF response category model. These baseline covariates were pre-specified for assessment in the design of the MADIT-CRT trial (12). Thresholds for categorization of numeric variables were pre-specified using accepted clinical and laboratory criteria. In univariate analysis of covariates of interest and LVEF response category, continuous variables were analyzed using the nonparametric Kruskal-Wallis test and categorical variables were analyzed using the chi-square test. Multivariate logistic regression was used to determine predictors of super-response. The pool of variables considered were those found to be significant at a pre-specified $p < 0.10$ in univariate analysis. A best-subset regression procedure was used to develop the model using the best chi-square statistic for each given number of variables. The largest model that had at least 3.84 gain in the chi-square score above the next smallest model was chosen and then refit to ensure that all variables met the significance level of <0.05.

For analysis of the association of LVEF response category and clinical outcomes, Kaplan-Meier estimates for nonfatal HF event or all-cause death (primary endpoint) as well as all-cause death (secondary endpoint) and all-cause death or ICD therapy for ventricular tachycardia or ventricular fibrillation (secondary endpoint) across echocardiographic response categories were determined and statistically evaluated with the log-rank test. Cox proportional hazards regression analyses were performed to assess the predictors of the primary endpoint (HF or all-cause death). A multivariate model for the primary endpoint was developed with Cox proportional hazards regression using the same potential pool of covariates as the multivariate logistic regression analysis discussed previously, with the addition of the LVEF response category (super-responder, responder, and hypo-responder). A best-subset regression method was used to build the model in the same manner as described, with a significance level set at 0.05. A likelihood ratio test was used to examine the added utility of the 12-month echocardiographic LVEF response variable. Checks for validity of the proportional hazards assumption were performed. All p values reported were 2-sided with a pre-specified significance at $p < 0.05$. Analyses were performed with SAS software version 9.20 (SAS Institute Inc., Cary, North Carolina).

Results

Super-responders experienced a mean absolute LVEF increase of 17.5 ± 2.7%, with all super-responders improving their LVEF ≥14.5%; responders experienced a mean absolute LVEF increase of 11.1 ± 1.8% with an improvement of LVEF between 7.9% and 14.4%; hypo-responders experienced a mean absolute LVEF increase of 4.4 ± 3.2% with an improvement in LVEF of <7.9%. Of 752 patients included in the cohort, 182 patients achieved a near normalization of cardiac function, with an absolute LVEF ≥45% at 12 months. A large proportion of super-responders (n = 135 [71%]) achieved an absolute LVEF ≥45% at 12 months, compared with a smaller proportion of responders (n = 45 [12%]) and hypo-responders (n = 2 [1%]).

Table 1 presents baseline clinical, electrocardiographic, echocardiographic, and laboratory characteristics of super-responders, responders, and hypo-responders. Super-responders were more often female, had nonischemic HF etiology, had baseline LBBB, and had longer QRS duration on electrocardiogram (ECG). Super-responders were less apt to have had prior revascularization by coronary artery bypass grafting or percutaneous coronary intervention, prior myocardial infarction, prior smoking history, or prior ventricular arrhythmia requiring treatment.

Echocardiographic changes of LVEF, LV end-diastolic volume index, LV end-systolic volume index, and LA volume index (LAVI) by responder group are shown in Table 2. For each echocardiographic measurement, there were significant differences across responder groups ($p < 0.001$ for all comparisons). On average, super-responders had a 16.2 ± 5.0 ml/m^2 decrease in LAVI. There were less extreme decreases of LAVI in responders (13.3 ± 5.0 ml/m^2) and hypo-responders (7.9 ± 5.3 ml/m^2). Changes in chamber size and function within responder groups are summarized in Figure 1.

Predictors of LVEF super-response to CRT-D. Best-subset regression analysis in patients with paired echocardiograms available at baseline and 12-month follow-up identified 6 predictors associated with LVEF super-response to CRT-D therapy (Table 3). These predictors included female sex, no prior myocardial infarction, QRS duration of ≥150 ms, LBBB on baseline ECG, body mass index (BMI) <30 kg/m^2, and smaller baseline LAVI (per 1 unit of SD below the mean). Best-subset regression analysis to identify predictors associated with LV end-systolic volume index response, as defined by a similar quartile categorization used for LVEF, revealed that the same characteristics were predictive of response.

Clinical outcomes. In our study population, the primary endpoint of nonfatal HF event or all-cause death after the 12-month follow-up echocardiogram occurred in 70 patients, with a median follow-up of 15.2 months. The secondary endpoint of all-cause death occurred in 25 patients, and the secondary endpoint of all-cause death or ICD therapy for ventricular tachycardia or ventricular fibril-

Table 1 Baseline Clinical Characteristics of MADIT-CRT Patients With Paired Echocardiograms at Baseline and 12 Months by Responder Category

Baseline Characteristics	Hypo-responder (LVEF Change <7.9%) (n = 190)	Responder (LVEF Change 7.9%–14.4%) (n = 371)	Super-Responder (LVEF Change ≥14.5%) (n = 191)	p Value
Age, yrs	63.6 ± 11.8	64.9 ± 10.5	64.2 ± 10.5	0.401
Women	33 (17)	77 (21)	75 (39)	<0.001
Race				
White	167 (88)	341 (92)	177 (93)	0.138
Black	18 (9)	24 (6)	10 (5)	0.242
Body mass index ≥30 kg/m^2	67 (36)	142 (39)	58 (31)	0.190
Enrolled from outside the United States	69 (36)	133 (36)	48 (25)	0.022
Ischemic NYHA functional class I	33 (17)	57 (15)	19 (10)	0.096
Ischemic NYHA functional class II	97 (51)	151 (41)	55 (29)	<0.001
Nonischemic NYHA functional class II	60 (32)	163 (44)	117 (61)	<0.001
Hypertension	120 (63)	241 (65)	115 (61)	0.586
Diabetes mellitus	54 (28)	118 (32)	45 (24)	0.117
Prior CABG surgery	71 (37)	103 (28)	36 (19)	<0.001
Prior PCI	64 (34)	103 (28)	41 (22)	0.031
Prior myocardial infarction	108 (57)	161 (44)	50 (27)	<0.001
Cerebrovascular accident	12 (6)	22 (6)	4 (2)	0.093
Previous cigarette smoking	104 (55)	215 (59)	90 (48)	0.050
Prior ventricular arrhythmias requiring treatment	20 (11)	28 (8)	7 (4)	0.035
Creatinine ≥1.4 mg/dl	44 (23)	87 (24)	37 (19)	0.527
LBBB	106 (56)	263 (71)	165 (86)	<0.001
RBBB	38 (20)	32 (9)	13 (7)	<0.001
QRS duration, ms	153.9 ± 18.1	159.7 ± 20.8	160.9 ± 17.4	<0.001
QRS duration ≥150 ms	107 (56)	238 (64)	148 (77)	<0.001
LVEDV index, ml/m^2	122.5 ± 25.5	126.4 ± 27.0	124.0 ± 24.7	0.215
LVESV index, ml/m^2	85.9 ± 20.3	90.2 ± 21.9	87.6 ± 20.6	0.064
LAV index, ml/m^2	44.5 ± 9.4	46.9 ± 10.2	43.7 ± 9.2	<0.001
Aldosterone antagonists	57 (30)	121 (33)	61 (32)	0.819
Amiodarone	14 (7)	28 (8)	8 (4)	0.286
Angiotensin-converting enzyme inhibitors	147 (77)	284 (77)	147 (77)	0.976
Angiotensin receptor blockers	39 (21)	82 (22)	37 (19)	0.740
Beta-blockers	173 (91)	348 (94)	185 (97)	0.061
Digitalis	57 (30)	96 (26)	47 (25)	0.446
Diuretics	136 (72)	262 (71)	120 (63)	0.109
Lipid-lowering statin drugs	131 (69)	270 (73)	109 (57)	<0.001

Values are mean ± SD or n (%).

CABG = coronary artery bypass grafting; LAV = left atrial volume; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RBBB = right bundle branch block.

Table 2 Echocardiographic Parameters in Patients Who Underwent Baseline and 12-Month Follow-Up Echocardiograms by Responder Category

	Hypo-responder (LVEF Change <7.9%)			Responder (LVEF Change 7.9%–14.4%)			Super-Responder (LVEF Change ≥14.5%)		
	N	Baseline	Change	N	Baseline	Change	N	Baseline	Change
LVEF, %	190	30.3 ± 3.3	4.4 ± 3.2	371	29.0 ± 3.2	11.1 ± 1.8	191	29.7 ± 3.3	17.5 ± 2.7
LVEDV index, ml/m^2	187	122.5 ± 25.5	−11.2 ± 10.1	367	126.4 ± 27.0	−26.5 ± 11.8	188	124.0 ± 24.7	−40.8 ± 16.8
LVESV index, ml/m^2	187	85.9 ± 20.3	−12.6 ± 10.7	367	90.2 ± 21.9	−29.8 ± 10.0	188	87.6 ± 20.6	−43.1 ± 13.4
LAV index, ml/m^2	187	44.5 ± 9.4	−7.9 ± 5.3	366	46.9 ± 10.1	−13.3 ± 5.0	188	43.7 ± 9.2	−16.2 ± 5.0

Values are mean ± SD.

Abbreviations as in Table 1.

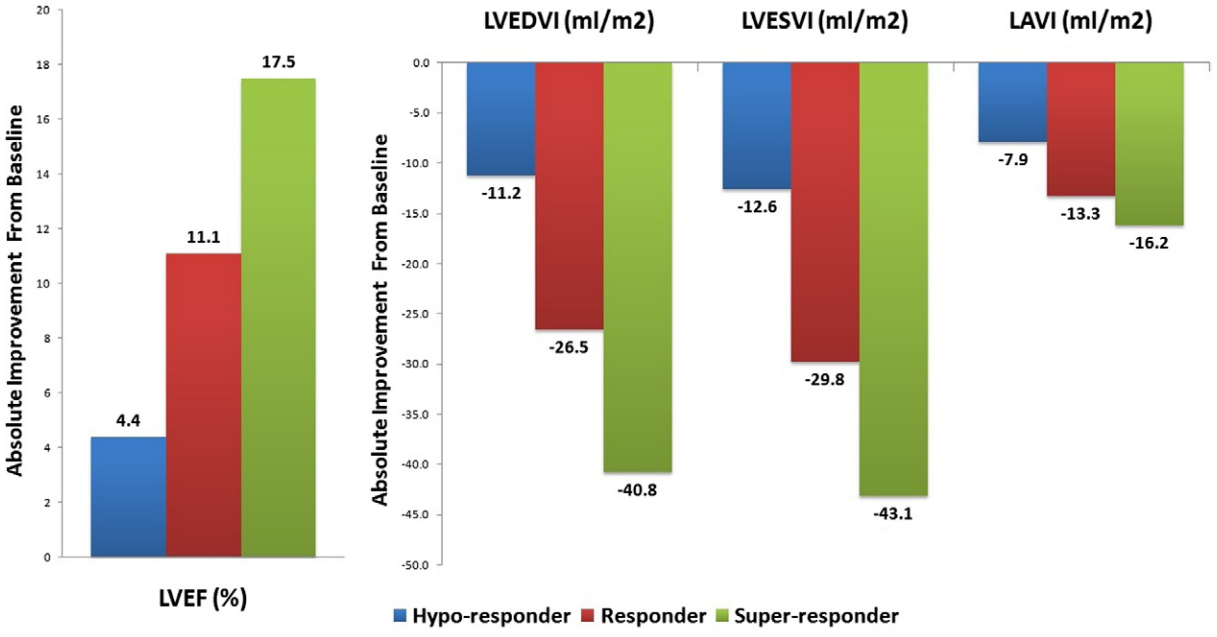

Figure 1 **Changes in Echocardiographic Parameters in Super-Responder, Responder, and Hypo-Responder Categories**

Changes in mean echocardiographic variables between baseline and 12-month follow-up among responder groups. LAVI = left atrial volume index; LVEDVI = left ventricular end diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end systolic volume index.

lation occurred in 99 patients. The primary endpoint occurred in 5 patients (2.6%) in the super-responder group, 29 patients (7.8%) in the responder group, and 36 patients (19.0%) in the hypo-responder group. The secondary endpoint of all-cause death occurred in 3 patients (1.6%) in the super-responder group, 10 patients (2.7%) in the responder group, and 12 patients (6.3%) in the hypo-responder group. The secondary endpoint of all-cause death or ICD therapy for ventricular tachycardia or ventricular fibrillation occurred in 10 patients (5.2%) in the super-responder group, 44 patients (11.9%) in the responder group, and 45 patients (23.7%) in the hypo-responder group. The effect of LVEF response to CRT-D and the cumulative probability of the primary and secondary endpoints by Kaplan-Meier analysis are shown in Figures 2A to 2C.

Table 3 **Multivariate Analysis of Predictors of LVEF Super-Response**

Variable	Odds Ratio	95% Confidence Interval	p Value
Female	1.96	1.32–2.90	0.001
QRS duration ≥150 ms	1.79	1.17–2.73	0.007
LBBB	2.05	1.24–3.40	0.006
Body mass index <30 kg/m^2	1.51	1.03–2.20	0.035
No prior myocardial infarction	1.80	1.20–2.71	0.005
Left atrial volume index, SD*	1.47	1.21–1.79	<0.001

*Per 1-U SD below mean.
Abbreviations as in Table 1.

To estimate the linear relationship between the 3-level LVEF response group and the primary endpoint of HF or all-cause death, a univariate Cox proportional hazards regression model with a single ordinal response group measure was fit and revealed a trend of increasing LVEF response group and lower hazard of the primary endpoint (hazard ratio [HR]: 0.36 [referent: lower response group]; 95% confidence intervals [CI]: 0.25 to 0.53; $p < 0.001$ for trend). A similar model for the all-cause mortality endpoint was also estimated, with a similar trend seen of lower hazard of the secondary endpoint with increasing LVEF response group (HR: 0.44 [referent: lower response group]; 95% CI: 0.24 to 0.83; $p = 0.011$ for trend). Finally, a model for the secondary endpoint of all-cause death or ICD therapy for ventricular tachycardia or ventricular fibrillation was estimated, and again, a similar trend of lower hazard of the secondary endpoint with increasing LVEF response group was seen (HR: 0.43 [referent: lower response group]; 95% CI: 0.32 to 0.59; $p < 0.001$ for trend).

Including LVEF response category as a potential covariate, a best-subset regression procedure using Cox proportional hazards multivariate regression was performed to assess predictors of the primary endpoint of HF or all-cause death (Table 4). Hyporesponse was associated with an increased risk of HF or all-cause death as compared with super-response (HR: 5.25; 95% CI: 2.01 to 13.74; $p = 0.001$). A baseline creatinine of ≥1.4 mg/dl was also associated with an increased risk of the primary endpoint

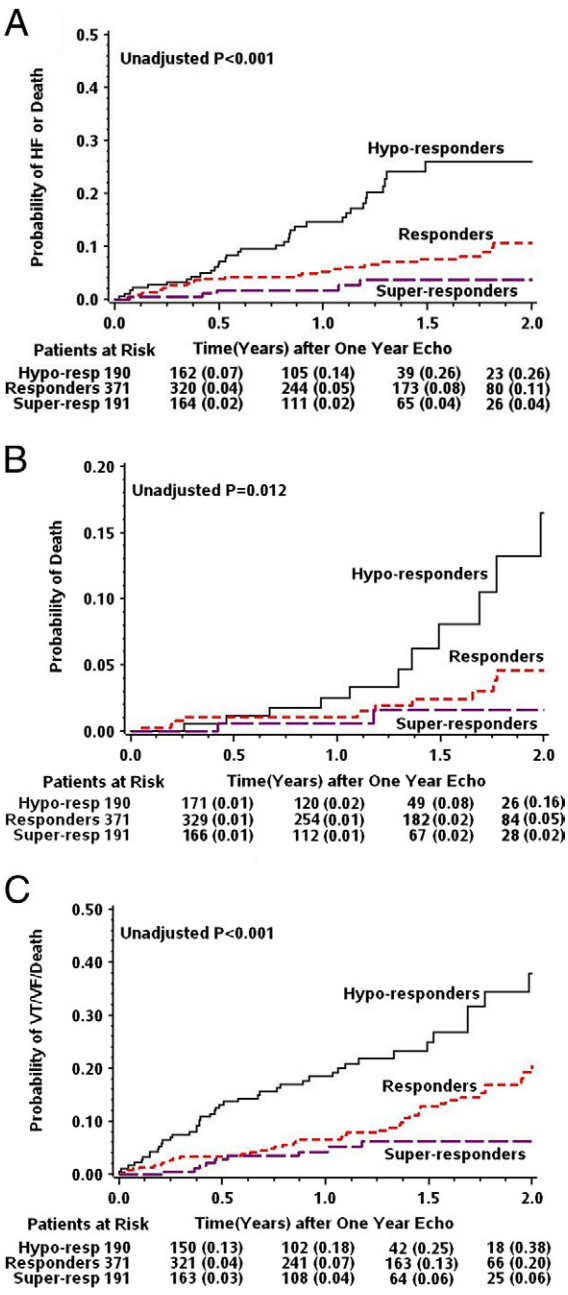

Figure 2 **Kaplan-Meier Estimates of Cumulative Probability of Heart Failure or Death, Death Alone, and Death or ICD Therapy for VT or VF Stratified by Response Category**

The 3 curves reflect the probability of outcome over time by response category in cardiac resynchronization therapy with defibrillator patients with baseline and 12-month follow-up echocardiograms, after the 12-month follow-up echocardiogram time point. **(A)** For the primary endpoint of heart failure or all-cause death, super-responders **(purple line)** performed the best compared to responders **(red line)** and hypo-responders **(black line)**. **(B)** For the secondary endpoint of all-cause death, super-responders **(purple line)** also did the best compared to responders **(red line)** and hypo-responders **(black line)**. **(C)** For the secondary endpoint of all-cause death or ICD therapy for VT or VF, super-responders **(purple line)** again fared the best compared to responders **(red line)** and hypo-responders **(black line)**. ICD = implantable cardioverter-defibrillator; HF = heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia.

(HR: 3.02; 95% CI: 1.66 to 5.49; $p < 0.001$), whereas baseline LBBB was associated with a decreased risk of HF or all-cause death (HR: 0.57; 95% CI: 0.34 to 0.94; $p = 0.029$). A likelihood ratio test was used to compare the fit of the data with the addition of the LVEF response category variable over the baseline model, which showed a significant difference ($p < 0.001$). Thus, adding the LVEF responder variable to the baseline model significantly improved the predictive power of the model.

Discussion

The present study, composed of patients with mildly symptomatic HF in the MADIT-CRT study, identified specific predictors of LVEF super-response to CRT-D and found super-response to be associated with reduced risk of subsequent cardiac events (HF or all-cause death). We identified 6 baseline clinical, electrocardiographic, and echocardiographic predictors of LVEF super-response in those assigned to CRT-D. These predictors included female sex, no prior myocardial infarction, QRS duration ≥150 ms, LBBB on baseline ECG, BMI <30 kg/m^2, and smaller LAVI (per 1 unit of SD below the mean). The cumulative probability of HF or all-cause death, all-cause death alone, and all-cause death or ICD therapy for ventricular tachycardia or ventricular fibrillation differed significantly across LVEF response categories at 2 years of follow-up, with improved event-free survival based on extent of response. When LVEF response was included as a potential predictor of the primary endpoint of HF or all-cause death in multivariate analysis, LVEF hyporesponse (compared with super-response) and a baseline creatinine of ≥1.4 mg/dl were associated with an increased risk of subsequent HF or all-cause death, whereas LBBB on baseline ECG was associated with a decreased risk of HF or all-cause death. These findings suggest that easily identifiable baseline factors are associated with LVEF super-response on 12-month follow-up echocardiogram in patients with mildly symptomatic HF that meets other indications for CRT-D. Further, LVEF response itself may predict subsequent clinical outcomes, including HF or all-cause death.

LVEF is used to guide therapy and evaluate patient response to HF treatments. Reduced LVEF is associated

Table 4 **Cox Proportional Hazards Regression Analysis of Predictors of Nonfatal Heart Failure Event or Death**

Variable*	Hazard Ratio	95% Confidence Interval	p Value
LVEF response†			
Super-responder	Reference	—	—
Hypo-responder	5.25	2.01–13.74	0.001
Responder	2.24	0.86–5.83	0.099
LBBB	0.57	0.34–0.94	0.029
Creatinine ≥1.4 mg/dl	3.02	1.66–5.49	<0.001

*Stratified by ischemic status. †The likelihood ratio test with 2 degrees of freedom testing the responder and hypo-responder variables had a p value < 0.001.
Abbreviations as in Table 1.

with risk of ventricular arrhythmia and sudden death; as a result, randomized controlled trials and guidelines for prophylactic defibrillator implantation to prevent sudden death have relied heavily on this measurement (instead of volume measurements, from which it is derived) to qualify for device candidacy (15). Given the clinical reliance on LVEF as an indication for therapy and for assessing response to CRT-D therapy, we justified the classification of responsiveness to CRT-D on the extent of improvement in ejection fraction among patients enrolled in the MADIT-CRT trial. In our study, super-responders, on average, experienced an 18 percentage point absolute improvement in LVEF.

LVEF is easily obtained, universally used by clinicians, and associated with clinical outcomes, rendering it one of the most widely used metrics to define response to CRT. However, the heterogeneity in cardiac remodeling and clinical response in patients who receive CRT-D therapy also highlights the need to establish baseline factors to predict which patients will derive the greatest benefit. Predicting super-response is important given the findings of our study, which suggest that the extent of improvement in LVEF at 12 months after CRT-D implantation itself provides important prognostic information. LVEF super-response at this time point is associated with a subsequent decreased cumulative probability of HF or all-cause death, all-cause death alone, and ICD therapy for ventricular tachycardia or ventricular fibrillation in a mildly symptomatic HF population.

Our study of patients from the MADIT-CRT trial differs from previous work evaluating clinical outcomes in super-responders in that data were collected prospectively, at multiple centers, and in a larger group of patients with HF (10,16). Additionally, the MADIT-CRT study enrolled patients with less severe HF (NYHA class I to II), whereas previous studies included patients with more severe HF (NYHA class III to IV). In our study, LVEF super-response was defined at 12 months instead of 6 months, which may have allowed more time for a true super-responder effect to be realized. The findings of our study suggest that LVEF can be used to define super-responders to CRT-D therapy in a mildly symptomatic HF population, and most importantly, that LVEF super-response is associated with improved clinical outcomes by responder category. The determinants of failure to respond to therapy and the associated worse outcomes are likely based on a number of variables that were not addressed in this study. Whether more aggressive medical therapy, adjustment of CRT-D parameters, or other adjunctive therapies will promote additional reverse cardiac remodeling in hypo-responders at 12 months and beyond and whether these strategies improve clinical outcomes are areas for future research.

In this study of patients assigned to CRT-D in the MADIT-CRT cohort with available baseline and 12-month follow-up echocardiograms, of the 6 predictors of super-response identified, baseline LBBB (6,10) and smaller LA volume (9) were previously identified as predictors of LVEF super-response or hyper-response, but in mostly advanced HF populations (with NYHA class III and IV symptoms). Female sex and prolonged QRS duration have also been previously associated with overall improvement in cardiac remodeling in other studies of CRT, but again mostly in patients with advanced HF (17,18). Our findings coincide with subsequent studies of the MADIT-CRT mild HF population, which showed that women compared with men (19) and patients with baseline LBBB compared with non-LBBB (20) had improved echocardiographic parameters, including LVEF in those assigned to CRT-D versus ICD. However, our study further detailed the different levels of LVEF response found in MADIT-CRT patients assigned to CRT-D and identified other predictors of this response.

Lack of prior myocardial infarction predicted LVEF super-response in our study. It is possible that the association of no prior myocardial infarction and LVEF super-response is mediated by absence of LV scar, which was not specifically investigated in the MADIT-CRT study. Previous studies on the effect of scar and response to CRT have been contradictory (21,22). Regardless of the mechanism, our study showed that in multivariate analysis, absence of prior myocardial infarction predicts LVEF super-response to CRT. That CRT response in multivariate analysis was associated with lack of prior myocardial infarction but not the etiology of cardiomyopathy (ischemic vs. nonischemic) suggests possible confounding by prior myocardial infarction in the relationship of cardiomyopathy etiology and CRT super-response.

We also found that BMI <30 kg/m^2 predicted LVEF super-response. To our knowledge, this is the first study to associate a lower BMI with cardiac reverse remodeling attributed to CRT-D therapy. Because BMI is a complex variable composed of both height and weight, assessing its association with LVEF response may prove difficult. For example, human weight composition varies person to person and can be influenced by lean body mass, adiposity, and volume overload, particularly in an HF population. Additionally, our findings contrast with previous studies reporting an "obesity paradox" of BMI and HF outcomes, such that higher BMI was associated with improved HF outcomes (23). We found that lower BMI was associated with LVEF super-response, which itself was associated with improved clinical outcomes. Future studies of response to CRT-D therapy should focus on the determinants of BMI and associations with cardiac remodeling. In addition, whether a lower BMI predicts LVEF response to CRT-D is specific to a mildly symptomatic HF population, such as the one studied in the MADIT-CRT trial, is unknown and deserves further investigation.

Study limitations. The study protocol of follow-up echocardiograms obtained at 12 months rendered us unable to determine the timing of improvement in LVEF before 1 year. As a result, we were unable to determine if the rapidity with which ejection fraction improved was associated with clinical outcome. We were also unable to assess predictors of delayed improvement of LVEF and outcomes associated with late improvement. Additionally, the short duration of

follow-up in this study should be considered a limitation of the present analysis. After the 12-month echocardiogram, which categorized patients into LVEF responder groups, the average follow-up time was 15.2 months. Given the brief follow-up time and the small number of events, longer follow-up is warranted. Assignment to CRT-D response category was dependent on echocardiographic measurement of LV volumes and calculation of LVEF. The high level of reproducibility in measuring LVEF in our study may not be as precise in other clinical settings and may reduce the generalizability of these results. Finally, our study focused intentionally on patients assigned to CRT-D therapy, with baseline and 12-month follow-up echocardiograms. Therefore, patients who died or were lost to follow-up before the 12-month echocardiogram were not included in our analysis. Although there were few patients who were lost to follow-up or died in the first 12 months, it is possible that selection bias may have been introduced (i.e., patients with lower LVEF or no response may have been more likely to die or be lost to follow-up for the 12-month echocardiogram, therefore selecting for a super-response group less likely to experience subsequent HF or death).

Conclusions

Findings from the MADIT-CRT trial suggested that LVEF super-response at 12-month follow-up echocardiogram was associated with improved HF event-free survival after 2 years in CRT-D patients with mild HF symptoms. In this same patient population, female sex, no prior myocardial infarction, QRS duration of ≥150 ms, LBBB, BMI of <30 kg/m^2, and smaller baseline LAVI predicted LVEF super-response to CRT-D. Our observations suggest that certain baseline factors may predict LVEF super-response for this population and that LVEF super-responders may enjoy freedom from subsequent HF or all-cause death, even for those with mild HF symptoms at the time of CRT-D implantation.

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Key Words: cardiac resynchronization therapy ■ heart failure ■ pacing ■ super-response.